

ACC.24 Late-Breaking Science Poised to Have Significant Impact on CV Care

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ACC.24 featured 23 Late-Breaking Clinical Trials (LBCTs), covering a spectrum of topics including heart failure, hypertension, dyslipidemia, coronary artery disease, valvular heart disease, cardiomyopathy and cardiac rehabilitation. The findings of these studies are poised to have a significant impact on the field of cardiovascular medicine, providing pivotal guidance for future clinical practice in cardiovascular care.

Acute myocardial infarction (AMI) patients still face a high risk of recurrent ischemic events. Given the inverse correlation between HDL-C levels and atherosclerotic cardiovascular disease risk, efforts have been made over the years to reduce residual atherosclerotic cardiovascular disease risk by raising HDL-C levels. However, neither niacin nor cholesterylester transfer protein inhibitors, which elevate HDL-C levels, have succeeded in lowering cardiovascular event risk. Consequently, attention has shifted from raising HDL levels to improving HDL functionality. CSL112 is human apolipoprotein A1 derived from plasma that increases HDL-mediated cholesterol efflux capacity and demonstrates favorable safety upon infusion.

AEGIS-II represents the first clinical trial to assess whether increasing cholesterol efflux capacity can reduce the risk of major adverse cardiovascular events. Disappointingly, the study failed to demonstrate a significant reduction in cardiovascular death, any myocardial infarction or stroke risk with CSL112 intravenous therapy in high-risk AMI patients. This underscores the lack of evidence supporting the effective improvement of cardiovascular outcomes through either HDL quantity or function. The setback in HDL-C intervention suggests that our understanding of HDL may still be incomplete, necessitating comprehensive and in-depth research to validate the efficacy of the "HDL hypothesis" in the future.

Hypertriglyceridemia is common, but there are limited treatment that can effectively reduce triglyceride rich lipoprotein. Severe hypertriglyceridemia can lead to recurrent acute pancreatitis. In addition, triglyceride rich lipoprotein per unit particle seems to have the same atherogenic potential as LDL-C. Observational and Mendelian randomized studies have shown that hypertriglyceridemia has a strong correlation with atherosclerosis and ischemic events in the entire vascular region. Traditional triglyceride-lowering drugs such as beta, niacin and ω -3 fatty acids usually have limited ability, ranging from 15% to 40%, which has little impact on patients with severe hypertriglyceridemia or hereditary THG. Therefore, people have begun to focus on developing new drugs that can significantly reduce triglyceride and triglyceride rich lipoprotein.

Among these new drugs, antisense oligonucleotides targeting apolipoprotein C-III (APOC3) mRNA is one of the most promising drugs. The second-generation antisense oligonucleotides formulation targeting APOC3 mRNA (Volanesorsen) has been proven in phase 3 clinical trials

to reduce circulating TG levels by 70% in patients with familial hypercholesterolemia. However, thrombocytopenia and injection site reactions are common, so it has not been approved by the U.S. Food and Drug Administration for clinical use. Olezarsen, as a third-generation antisense oligonucleotides formulation targeting APOC3 mRNA, coupled with N-acetylgalactosamine, can selectively inhibit liver APOC3, resulting in higher safety. The results of the BRIDGE-TIMI 73a study showed that Olezarsen can reduce triglyceride levels by about 50%, and clinically significant abnormalities of liver, kidney or platelet are not common. Importantly, in patients with high cardiovascular risk associated with hypertriglyceridemia, Olezarsen can also reduce apoB levels, and the cardiovascular benefits of this drug are expected to be observed in future phase 3 clinical studies.

Most trials that have demonstrated the benefits of using β receptor blockers after myocardial infarction were mainly aimed at patients with large-area myocardial infarction and were conducted in the era before modern biomarker based on diagnostic methods and percutaneous coronary intervention, antithrombotic drugs, high-intensity statins and renin angiotensin aldosterone system antagonists. The current guidelines recommend the use of β receptor blockers in patients after myocardial infarction (unless contraindications exist). However, a meta-analysis showed that the use of β receptor blockers in modern reperfusion strategies did not significantly reduce mortality.

The research results of REDUCE-AMI showed that long-term use of β receptor blockers did not reduce the risk of all-cause mortality or new onset myocardial infarction as the primary endpoint in acute myocardial infarction (AMI) patients undergoing early coronary angiography with preserved ejection fraction (LVEF \geq 50%). The negative result of this study may change the medication decisions of many doctors regarding AMI patients. However, we must be aware of the limitations of a single registration based, somewhat ineffective open label study. It may still be too early to explicitly remove β receptor blockers from the "secondary prevention ladder", and further validation through larger randomized controlled trials is needed in the future.

Hypertrophic cardiomyopathy (HCM) is a common hereditary cardiomyopathy. Although significant progress has been made in the treatment of symptomatic obstructive HCM, effective targeted drugs are currently lacking for symptomatic non-obstructive HCM patients. Nineraxstat is a novel cardiac mitotrope agent, which can partially inhibit fatty acid oxidation, shifting cardiac energy metabolism from free fatty acid oxidation to glucose oxidation, thereby improving cardiac oxygen utilization efficiency and effectively restoring myocardial energy homeostasis.

The results of the phase 2 IMPROVE-HCM study showed that nineraxstat was safe and well tolerated in symptomatic non-obstructive HCM patients, and might have a positive impact on exercise performance, cardiopulmonary function and quality of life. Results suggested that nineraxstat had a certain potential in the treatment of non-obstructive HCM, providing a basis for further large-scale phase 3 clinical trials. With ongoing research and the accumulation of clinical data in the future, the prospects of nineraxstat in the treatment of non-obstructive HCM are promising.

Transcatheter aortic-valve implantation (TAVI) is increasingly performed in patients with

severe, symptomatic aortic-valve stenosis (AS). In patients at high surgical risk or elderly patients (regardless of surgical risk), TAVI is the preferred treatment option. However, in patients at low or intermediate surgical risk who are eligible for both TAVI and SAVR, the optimal treatment strategy remains controversial. The results of the DEDICATE-ZHK6 study showed that among patients with severe AS at low or intermediate surgical risk, TAVI was noninferior to SAVR with respect to death from any cause or stroke at one year, providing more clinical evidence for the choice of treatment strategy for patients with severe AS. Compared to previous studies, the DEDICATE-DZHK6 study was closer to the real world and aimed to reflect the current state of the therapy for severe AS.

Results of the study will help to further determine the optimal treatment strategy for patients at low or intermediate risk who are suitable for both TAVI and SAVR. However, the long-term effects of TAVI are still unclear at present. It is hoped that there will be more long-term follow-up data in the future, not only to confirm the effectiveness and safety of TAVI, but also to conduct more detailed observation and analysis of the performance of bioprosthetic valves used in TAVI, including valve degeneration, subclinical thrombosis, hemodynamic data and more.

It is certain that the cutting-edge advancements in the cardiovascular field presented at ACC.24 will have a profound impact on the prevention, treatment and scientific research of cardiovascular diseases in China. Let us reconvene next year in the "hometown of skyscrapers" and anticipate another exciting annual scientific session!

ACC.25 will be held March 29-31, 2025, in Chicago, IL.

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